New Approach in Prevention of Shivering with Spinal Anesthesia

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Abstract

Background: Shivering during spinal anesthesia is a multifactorial challenge triggered by factors such as cold environments and vasodilation, leading to discomfort, increased oxygen consumption, and potential surgical complications. Effective prevention and management strategies are essential to ensure patient well-being. This review article explores a range of methods, including non-pharmacological and pharmacological approaches, for shivering prevention during spinal anesthesia, considering patient-specific factors and potential side effects, while also highlighting recent advancements in this field and their clinical implications. **Objective:** The aim of this review article is to provide a comprehensive overview of recent advancements and approaches in the prevention of shivering during spinal anesthesia. It explores the mechanisms underlying shivering, discusses a wide range of pharmacological interventions, highlights non-pharmacological strategies, and offers insights into clinical considerations. **Conclusions:** Shivering during spinal anesthesia remains a significant concern, but recent developments in both non-pharmacological and pharmacological methods offer promising avenues for prevention and management.

Keywords: Shivering; Spinal Anesthesia; Prevention; Pharmacological Methods; Non-Pharmacological Methods; Clinical Considerations.

1. Introduction

Shivering is an involuntary somatic motor response triggered by exposure to cold environments or fever. It serves to generate heat and involves the contraction of skeletal muscles [1]. This response is controlled by brain mechanisms, particularly the median preoptic nucleus (MnPO), as evidenced by experiments monitoring parameters like brown adipose tissue (BAT) temperature, arterial pressure, and heart rate. Acute skin cooling consistently increases EMG, BAT temperature, and heart rate, all of which can be inhibited by muscimol nano-injection into the MnPO [2, 3].

The most common causes of shivering include fever, shivering with spinal anesthesia, movement disorders, postanesthetic shivering, fear, excitement, stress, tremors, low blood sugar, anxiety, and shivering. Shivering with spinal anesthesia is an involuntary, oscillatory muscular activity that significantly increases metabolic heat production, potentially reaching up to 600% above the basal metabolic level [4]. The exact mechanisms underlying post-spinal shivering are not fully understood but may

involve thermoregulatory responses to hypothermia, affecting neurons in specific brain regions.

To prevent shivering during spinal anesthesia, various methods can be employed: Non-pharmacological methods: For non-hypothermic patients, monitoring vital signs may be sufficient. Hypothermic patients can benefit from passive or active warming procedures performed at least 30 minutes before the operation. Passive methods involve external thermal insulation or warm blanket application, while active methods include the use of heat transfer mechanisms, such as warm air or water-based systems, as well as warm intravenous or irrigation fluids [5].

Pharmacological methods: Several medications can be used to prevent shivering during spinal anesthesia, including Ketamine, Phenylephrine, Ondansetron, Tramadol, Pethidine, Granisetron, Dexmedetomidine, Nalbuphine, Clonidine, Magnesium sulfate, Propofol and Dexamethasone [6, 7].

The aim of this study is to discuss the recent methods to prevent shivering with spinal anesthesia.

2. Shivering with Spinal Anesthesia

Shivering frequently occurs as a complication of anesthesia, especially following spinal anesthesia, with reported incidence rates of up to 50-65%. The mechanism underlying shivering during spinal anesthesia is primarily vasodilatation, leading to rapid heat loss and a shift of body heat from the core to peripheral tissues, resulting in hypothermia and subsequent shivering. This phenomenon can increase oxygen consumption, posing risks of hypoxemia and complications in the postoperative phase [8].

Pathophysiology

Shivering serves as a physiological response to cold exposure, triggered as a means of preserving heat after peripheral vasoconstriction. It often presents as an involuntary, oscillatory muscular activity during early post-anesthetic recovery. Shivering can vary in intensity, ranging from isolated facial or muscle group fasciculations to full-body involvement. Its incidence varies across different anesthesia procedures. The pathophysiology of shivering involves cooling of the preoptic region of the hypothalamus, with efferent signals traveling through the medial forebrain bundle and spinal alpha motor neurons. Cold stimulation recruits motor neurons in a specific sequence, leading to the observed rhythmic pattern of electromyographic discharges during shivering [9].

Etiology

The etiology of shivering is multifactorial, with various causes including thermoregulatory impairment due to anesthesia, exposure to a cool environment, pain,

disinhibited spinal reflexes, decreased sympathetic activity, and respiratory alkalosis. Despite being often associated with hypothermia, shivering can also occur in normothermic patients during the perioperative period. Shivering has both thermoregulatory benefits and adverse effects [10]. While it helps raise core body temperature, it also places the body under increased physiological stress, potentially doubling oxygen consumption and leading to increased catecholamine release, cardiac output, heart rate, and arterial pressure. It can interfere with monitoring during anesthesia and postoperative care, affecting patient comfort and satisfaction [11].

Grading and mechanisms

Shivering can be graded to assess its severity and impact on patient well-being. Various scales have been proposed, ranging from assessing muscle activity to interference with monitoring or causing patient distress. The neurophysiology of shivering involves complex mechanisms, including thermosensors, neural pathways, and central integration in the hypothalamus. The efferent shivering pathway originates in the hypothalamus and ends at motor neurons [12].

3. New Approach in Shivering Prevention (Non-Pharmacological and Pharmacological Methods)

Shivering with spinal anesthesia is a common and distressing complication of surgery, often caused by postoperative pain and hypothermia. Recognizing the importance of maintaining normal body temperature during and after anesthesia, effective treatment strategies have become essential. While various therapeutic approaches exist, most are empirical, and the overall quality of antishivering guidelines is limited. Shivering occurs in diverse settings and with varying durations and intensities, necessitating tailored treatment algorithms. The American Society of Anesthesiologists recommends forced-air warming devices and meperidine as effective strategies, leading to two main approaches: pharmacological and nonpharmacological methods [13].

A. Non-pharmacological therapy

Non-pharmacological therapy is often favored over medications for managing shivering due to the potential adverse effects of drugs in clinical settings. These methods aim to maintain or elevate body temperature above the shivering threshold or suppress the central shivering reflex by providing warm sensory input through the skin. Active cutaneous warming, including electric heating, water-circulating garments, forced-air, and radiant heating, is particularly effective in perioperative and induced hypothermia scenarios. Passive cutaneous warming and core warming methods, such as heated fluids and heated air, offer limited benefits [14]. Active cutaneous warming, by increasing body heat content and minimizing heat redistribution, interferes with cutaneous thermoreceptors and effectively controls thermoregulatory shivering. Upper body forced-air warming has shown efficacy in caesarean deliveries, emphasizing the

need for preoperative warming before sympathetic-mediated vasodilation and core-periphery redistribution [15].

B. Pharmacological therapy

Pharmacological therapy offers various options for preventing and treating shivering with spinal anesthesia, including opioids, α2-agonists, anticholinergics, central nervous system stimulants, and corticosteroids. These medications target different levels of the complex thermoregulatory control loop, involving thermal receptors, spinal cord, brainstem, anterior hypothalamus, and cerebral cortex. Highly effective medication classes include centrally acting analgesics (tramadol), opioid receptor agonists (meperidine, fentanyl), cholinesterase inhibitors (physostigmine), and N-methyl-D-aspartate receptor antagonists (ketamine, magnesium sulfate) [15]. In contrast, α2-central agonists (clonidine, dexmedetomidine), antiserotonergic agents (ondansetron), and anti-inflammatory drugs (dexamethasone) are relatively less effective. However, some medications have potential side effects, such as clonidine's association with bradycardia, hypotension, and sedation, and ondansetron's use for preventing postoperative nausea and vomiting. Nonetheless, systematic tracking of medication side effects remains limited in most studies [16].

- **Opioid receptor agonists**

❖ Meperidine

Meperidine, an opioid receptor agonist, has demonstrated therapeutic effectiveness in preventing and treating shivering with spinal anesthesia. Its mechanism of action involves activation of κ and μ-opioid receptors within the central nervous system, particularly the κ receptor, reducing the shivering threshold and lowering core temperature [17]. Meperidine is commonly used intravenously for shivering management due to its superior equi-analgesic dose compared to other opioids like fentanyl, alfentanil, sufentanil, or morphine. However, its use can be associated with side effects, including an increased risk of nausea, vomiting, and respiratory depression. Intrathecal pethidine, while effective in reducing shivering during cesarean section under spinal anesthesia, may also increase the incidence of nausea and vomiting [18]. Different studies have explored the optimal dose of intrathecal pethidine for shivering prevention, with varying results and considerations of side effects, emphasizing the need for further research to determine the best approach for managing shivering with spinal anesthesia, especially in the context of different dose levels and their impact on shivering and side effects [19].

❖ Tramadol

Tramadol, a unique analgesic with dual mechanisms involving the inhibition of noradrenaline and 5-HT3 reuptake, has been explored for its potential in shivering control. It is a racemic mixture of (+) dextro and (-) levo enantiomers and is considered

safer than other opioid analgesics in terms of respiratory depression and addiction [20, 21]. Tramadol's analgesic action is mediated through its weak μ-opioid receptor agonism, synergizing with its influence on serotonergic and noradrenergic receptors. The racemic mixture of enantiomers offers a synergistic analgesic effect, with the (+) enantiomer acting as a μ-opioid receptor agonist and the (-) enantiomer inhibiting noradrenaline reuptake. It is used mainly to treat muscle, joint, and wound pain, with some limitations regarding patient medical history. Tramadol's metabolism involves O- and N-demethylation, forming metabolites, of which O-desmethyl tramadol (M1) is particularly potent [22]. Despite its advantages, tramadol is not without side effects, including serotonin syndrome, seizures, hyperalgesia, and various central nervous system, gastrointestinal, dermatologic, genitourinary, cardiovascular, metabolic, and musculoskeletal disturbances [23].

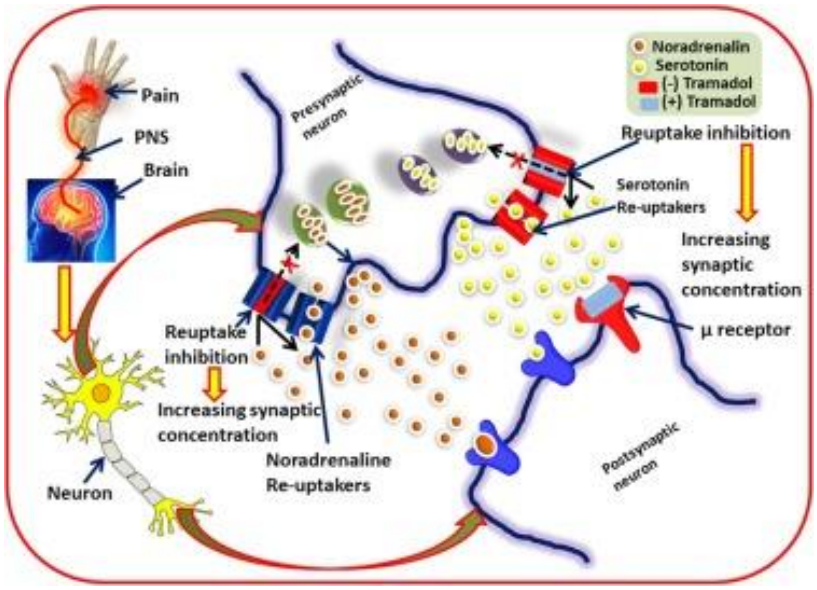

Figure 1: Schematic representation of MOA of Tramadol [21]

The mechanism of tramadol's action in shivering control is multifaceted, involving its effect on central neurotransmission. Its modulation of 5-HT3 and noradrenergic receptors, impacting the nucleus raphe magnus and inhibitory pathways, contributes to its antishivering efficacy [24]. The racemic mixture's synergistic effect on analgesia and temperature regulation, along with its ability to inhibit serotonin and noradrenaline reuptake, further supports its potential in shivering management. Tramadol's clinical utility in controlling post-anesthetic shivering has been compared favorably to pethidine, particularly within the first 30 minutes post-administration, with tramadol showing a lower recurrence rate. Core temperature may influence response rates, as lower core temperatures were associated with reduced efficacy. Overall, tramadol's antishivering effect, combined with its safety profile, makes it a promising option in managing shivering during anesthesia [25].

- **Nalbuphine**

Nalbuphine is widely employed in clinical surgery for its analgesic properties, but its high dosage has been linked to an increased risk of normeperidine toxicity, prompting the exploration of new drugs for post-anesthetic shivering management. Nalbuphine exerts its anti-shivering effect through its κ-receptor and α2-receptor activities, possessing both μ-antagonist and κ-agonist characteristics. This synthetic opioid demonstrates a high affinity for κ-opioid receptors in the central nervous system. Studies have shown that intravenous nalbuphine effectively treats shivering, exhibiting a higher success rate and faster cessation of shivering compared to dexmedetomidine. Furthermore, nalbuphine has a lower incidence of bradycardia and excessive sedation following treatment, making it a valuable option for managing shivering without causing respiratory depression, particularly in spinal anesthesia settings [26, 27].

- **Antiserotonergic agents**

5-HT3 receptor antagonists, a relatively recent addition in the realm of shivering prevention, have gained prominence due to the potential side effects associated with both opioid and non-opioid drugs used for shivering management. These antagonists have demonstrated efficacy in preventing shivering, with meta-analysis findings suggesting comparable effectiveness to meperidine. The mechanism of action involves inhibiting the reuptake of 5-HT in the preoptic area of the hypothalamus, where 5-HT3 is released to activate heat production pathways and raise body temperature. Consequently, 5-HT3 receptor antagonists prove effective in preventing shivering following both general anesthesia and spinal anesthesia [28].

- **Ondansetron**

Ondansetron, a 5-HT3 (serotonin) antagonist primarily used as an antiemetic, has been a subject of controversy regarding its effectiveness and safety in preventing shivering with spinal anesthesia. its mechanism of action may involve inhibiting 5-ht reuptake in the preoptic anterior hypothalamic region, influencing both heat production and heat loss pathways. studies have shown that both 4 mg and 8 mg of ondansetron administered at the end of surgery significantly reduce the risk of shivering with spinal anesthesia [29]. Furthermore, ondansetron exhibits similar antishivering effects to meperidine but with a lower risk of bradycardia and a significant association with a decreased risk of hypotension, as supported by meta-analysis findings, suggesting its safe and potentially shiver-reducing use [30].

In contrast to ondansetron, palonosetron, a newer 5-HT3 antagonist, has not been found to influence perioperative hypothermia or postanesthetic shivering significantly, indicating differences in efficacy compared to ondansetron in this context. Additionally, research highlights the potential of low-dose ketamine and ondansetron in preventing shivering during spinal anesthesia, although comparative studies evaluating their use are limited [31]. The relative preservation of temperature observed in ketamine groups may be attributed to the vasoconstrictive action of ketamine, while

the difference in ondansetron's effectiveness between studies could be attributed to variations in dosage [32, 33].

❖ **Granisetrone**

Granisetron, a potent 5HT3 receptor antagonist, has gained attention for its minimal adverse effects compared to other antiemetic drugs and its potential in preventing post-spinal anesthesia shivering [34]. Research suggests that serotonin antagonism, influenced by Granisetron, can lower the human thermal set-range, thereby reducing metabolic cold defenses and discomfort associated with post-operative hypothermia [28]. Studies have shown the effectiveness of Granisetron in preventing shivering, with various doses such as 3 mg, 1 mg, or 40 μg/kg proving to be effective. Additionally, Granisetron has demonstrated effectiveness in preventing emetic symptoms during regional anesthesia [34].

Comparative studies have shown that Granisetron can effectively reduce the incidence and severity of perioperative shivering in a dose-dependent manner. It has also been associated with a reduced incidence of postoperative nausea and vomiting (PONV) and pruritus, with no significant difference observed between different doses of Granisetron [35]. Meta-analyses have further supported the efficacy of 5-HT3 receptor antagonists, including Granisetron, in preventing post-operative shivering, with comparable effectiveness to meperidine. However, more high-quality randomized controlled trials with larger sample sizes are still needed to draw definitive conclusions about the preventive efficacy of 5-HT3 receptor antagonists in perioperative shivering prevention [36, 37].

The same dose that we used in our study. Also, it was reported that dexmedetomidine infusion during surgery was effective in the prevention of post-anesthetic shivering in patients undergoing elective abdominal hysterectomy. It was found the incidence of shivering as 15% with dexmedetomidine and 55% with placebo following general anesthesia. A previous study results are similar to their study with the incidences being 10% and 56.7%, respectively. The lower incidence of shivering in the dexmedetomidine group may be related to the depression of the thermoregulation threshold [38].

In a study observed that dexmedetomidine effectiveness in suppressing postanesthesia shivering in patients who had undergone laparoscopic surgery during general anesthesia. They administered intravenous dexmedetomidine 1 μg/kg during the perioperative period. They noted that the incidence of shivering was significantly lower in the dexmedetomidine group and concluded that intravenous dexmedetomidine possesses antishivering properties and can reduce the occurrence of shivering [39].

Also a study reported a low incidence of shivering (2 in 31) following SA by heavy bupivacaine 0.5% plus 5 μg intrathecal dexmedetomidine for lower abdominal surgeries compared with 12 of 31 in the control group. The key factors that may

contribute to these differences are those that could increase shivering during SA. These factors are aging, sensory-block levels, temperatures of the intrathecal local anesthetics, intravenous fluids, and operation room. In another study, the age of patients in the two grouShivering with spinal anathesthia, ambient temperature of the operating and recovery rooms (22°C–26°C), temperatures of the intrathecal drugs, and intravenous solutions (room temperature) were comparable [40].

Anti-Inflammatory Drugs

Dexamethasone

Dexamethasone is a potent, long-term acting synthetic glucocorticoid class of steroid drugs that have anti-inflammatory and immunosuppressant properties. It is one of the most active glucocorticoids, being about 25 to 30 times as potent as hydrocortisone. It prevents thermoregulatory shivering via its central inhibitory effect on the thermoregulatory center and prevents non thermoregulatory shivering by its anti-inflammatory activity, i.e., antagonizing the activation of the inflammatory responses and release of cytokines during surgery [41].

Cholinesterase inhibitors

They are a class of medications that play a crucial role in medicine, particularly in the context of anesthesia and the treatment of specific medical conditions. These drugs primarily work by inhibiting the breakdown of acetylcholine, a neurotransmitter, leading to increased acetylcholine levels in the body. Physostigmine is one of the prominent cholinesterase inhibitors used for its therapeutic properties [42].

Uses:

Physostigmine is commonly employed in clinical settings to reverse the toxic effects of drugs or substances that have anticholinergic properties. Anticholinergic agents can cause a range of symptoms, including dry mouth, blurred vision, confusion, and delirium. Physostigmine's ability to increase acetylcholine levels counteracts these symptoms by restoring normal cholinergic function in the body. It is especially useful in the treatment of anticholinergic toxicity caused by medications or plants. Myasthenia gravis is an autoimmune disorder characterized by muscle weakness and fatigue. Cholinesterase inhibitors like physostigmine are used to improve muscle strength and neuromuscular function by increasing acetylcholine availability at the neuromuscular junction. This helps alleviate the symptoms of the condition and enhances muscle contractions [43].

Side Effects:

While physostigmine can be highly beneficial in certain situations, it is not without potential side effects. Common side effects may include: Physostigmine can slow down the heart rate, leading to bradycardia. This effect should be closely monitored in patients with pre-existing heart conditions. Gastrointestinal disturbances, such as nausea and vomiting, are possible side effects of physostigmine. Increased

acetylcholine levels may result in excessive salivation or drooling. Some individuals may experience profuse sweating as a result of increased cholinergic activity. In rare cases, excessive cholinergic stimulation can lead to muscle weakness or twitching. While uncommon, in high doses, physostigmine can potentially trigger seizures [44].

Role in shivering with spinal anaesthesia

Physostigmine, a cholinesterase inhibitor, has been explored for its potential role in addressing shivering that occurs during spinal anesthesia, although it is not as commonly used for this purpose as some other medications like ketamine or magnesium sulfate. The rationale behind using physostigmine for shivering with spinal anesthesia lies in its ability to increase the levels of acetylcholine, a neurotransmitter, in the body. Acetylcholine is involved in the transmission of nerve signals, including those related to muscle contractions and temperature regulation. By inhibiting the breakdown of acetylcholine, physostigmine can enhance cholinergic activity, potentially influencing the body's response to temperature changes and muscle tone [45].

However, it's important to note that the use of physostigmine for shivering with spinal anesthesia is not considered a first-line treatment. Other medications, such as opioids, N-methyl-D-aspartate (NMDA) receptor antagonists (e.g., ketamine), and centrally acting analgesics, are often preferred for this purpose due to their more established efficacy [45].

NMDA Receptor Antagonist

- **Ketamine**

Ketamine, a noncompetitive NMDA receptor antagonist, is a valuable medication for preventing and treating shivering during spinal anesthesia due to its effect on temperature regulation. By blocking NMDA receptors, ketamine reduces the body's sensitivity to temperature changes, helping to prevent shivering-related discomfort and complications during surgery. However, ketamine is not without potential side effects, including drowsiness, hallucinations, and delirium, especially at higher doses. Careful monitoring and dose adjustment are essential to balance its therapeutic benefits with minimizing adverse effects. Recent studies have explored its use in combination with ondansetron, demonstrating promising results in shivering prevention, but the potential for sedation and other side effects remains a consideration, limiting its widespread use in this context [45-47].

- **Magnesium sulfate**

Magnesium sulfate, commonly known as "mag sulfate," is a versatile medication used in medicine, including its role in preventing and managing shivering during spinal anesthesia. Acting as an N-methyl-D-aspartate (NMDA) receptor antagonist, similar to ketamine, it helps regulate the body's response to temperature

changes, reducing the likelihood of shivering during surgical procedures [48]. Magnesium sulfate is also employed in obstetrics to prevent and manage eclampsia, a condition characterized by seizures during pregnancy. It serves as a central nervous system depressant and muscle relaxant, aiding in controlling seizures associated with eclampsia. However, healthcare providers must monitor patients for potential side effects, including muscle weakness, respiratory depression, and low blood pressure, especially at higher doses [49].

Magnesium sulfate, functioning as a calcium antagonist and NMDA receptor antagonist, exhibits a dual effect by both centrally regulating temperature responses and acting as a mild muscle relaxant, potentially reducing shivering intensity. Infusion of magnesium sulfate during surgery has been shown to effectively reduce shivering associated with spinal anesthesia. While it may only slightly lower the shivering threshold, this is often sufficient to attenuate shivering, particularly in postoperative patients with core temperatures near the normal shivering threshold. Magnesium sulfate has also demonstrated its effectiveness in reducing postoperative nausea and vomiting (PONV) when administered during total intravenous anesthesia. However, its use requires careful consideration of dosing and monitoring to manage potential side effects [50].

- **α_2-receptor agonist**

Alpha$_2$ adrenergic agonist receptors, which can lead to reduced sympathetic activity and central regulation of vasoconstrictor tone, are a group of drugs that have been used to try to prevent shivering. According to the Cochrane review, there is evidence that clonidine and dexmedetomidine can reduce shivering, but patients given dexmedetomidine may be more sedated. However, the quality of this evidence is very low. The doses, methods and time of administration have a wide range of possibilities: orally or intravenous, intraoperatively or preoperatively [51].

It was concluded in a meta-analysis that dexmedetomidine shows superiority over placebo in the prevention of shivering, but not over other anti-shivering agents. The beneficial effect can be achieved through both intravenous and epidural injection. Nevertheless, the time interval between the last administration and the end of surgery should be less than two hours, which is about the half-life of dexmedetomidine. Regarding to the doses 1 mg/kg bolus is the most commonly used, 0.5 mg/kg i.v. might be sufficient for a preventive effect [52].

Dexmedetomidine suppresses the spontaneous firing rate of neurons, decreases the central thermosensitivity, and finally reduces the vasoconstriction and shivering thresholds. Undesirable effects are sedation, bradycardia, hypotension and a dry mouth. Nevertheless, due to its relatively high price and potential side effects, the use of dexmedetomidine is not recommended solely for the purpose of preventing shivering [52].

❖ Dexmedetomidine

Dexmedetomidine, a highly specific α2-adrenergic receptor agonist, effectively reduces the incidence and severity of shivering during regional anesthesia without significant adverse effects [53]. Its mechanism of action in preventing shivering is believed to be centrally mediated, although the exact mechanism of shivering during regional anesthesia is not fully understood [45]. Dexmedetomidine's unique profile as an anti-shivering agent includes its sedative effects, making it a valuable option for shivering prevention without causing excessive sedation, respiratory depression, or hemodynamic instability. It increases the shivering threshold and attenuates the neuroendocrine and hemodynamic responses to anesthesia and surgery, offering a well-rounded approach to managing shivering [38].

Different studies have reported various concentrations of dexmedetomidine for pain relief and shivering prevention, often used in combination with other agonists. Combining dexmedetomidine with remifentanil has been shown to reduce postoperative pain effectively, while a lower dose of dexmedetomidine (0.05 μg/kg/hour) has been considered a suitable choice for anti-shivering purposes, highlighting its versatility in different clinical scenarios [54].

❖ Clonidine

Clonidine, an α2 receptor agonist, effectively reduces the incidence of shivering and oxygen consumption during anesthesia recovery. Its anti-shivering mechanism involves actions at three levels [55]: the hypothalamus, locus coeruleus, and spinal cord. These actions lead to alterations in the thermoregulatory threshold for vasoconstriction, activation of α2 receptors at the spinal cord level, and the release of norepinephrine and other mediators. Studies have compared clonidine and tramadol for prophylactic use in controlling shivering post-spinal anesthesia [56], with clonidine showing a higher response rate and lower recurrence of shivering compared to tramadol [57]. However, tramadol has a higher incidence of nausea and vomiting, limiting its use for shivering control, making clonidine a preferred choice in some situations due to its efficacy and better tolerability [55].

❖ Neuromuscular blockade

Many TTM protocols suggest the use of an NMB to control shivering if all other approaches fail. A study conducted by Dupuis et al[29] found vecuronium better than pancuronium for reduction of shivering because vecuronium was not shown to increase myocardial work and was associated with fewer complications [58]. Neuromuscular blocking agents are associated with prolonged obscuration of the neurological examination, prolonged length of stay in the neurointensive care unit, and prolonged mechanical ventilation, increasing the risk of developing ventilator-associated pneumonia. The use of TTM may interfere with clinical monitoring of NMB because hypothermia alters the normal peripheral response to a train-of-four assessment.

Decreased responsiveness to monitoring and prolonged duration of effect with the NMB agents during hypothermia increase the risks of long-term adverse effects seen with NMBs [58].

- **Other drugs**

other drugs aimed at the treatment and prophylactic of shivering with spinal anathesthia have been found. physostigmine inhibits pas through cholinergic system, but it can also cause nausea and vomiting, increased heart rate and blood pressure. doxapram, used as a stimulant in respiratory failure, had been proven to be effective on shivering with spinal anathesthia, but accompanied with a distinct side effect on hemodynamics. hydrocortisone (1–2 mgkg−1 i.v.) provides effective prophylaxis against shivering in patients undergoing day care knee arthroscopy under general anaesthesia. Nefopam, a centrally acting analgesic inhibiting synaptosomal reuptake of several neurotransmitters: dopamine, NE and serotonin, is one of the most studied effective antishivering drugs [59].

Prophylactic administration of parecoxib produces dual effects on antishivering and postoperative analgesia. This implies that cyclooxygenase 2-prostaglandin E_2 pathways may be involved in the regulation of shivering [45].

- **Phenylephrine**

Phenylephrine, an alpha-1 adrenergic agonist, acts through potent vasoconstriction when administered intravenously or applied to mucosal membranes. Its effects on cardiac output and end perfusion are influenced by various factors, including dosing method, volume status, heart rate, autonomic tone, and cardiac conditions, leading to complex and variable outcomes [60]. While it can increase preload temporarily due to venoconstriction and raise systemic vascular resistance and afterload through arterial constriction, reflex bradycardia may offset its impact on cardiac output. However, phenylephrine's alpha-1 receptor stimulation can lead to baroreceptor-mediated reflex bradycardia, and its use may need to be reconsidered in hypotensive, bradycardic patients. Additionally, it has a role in ophthalmic applications, causing pupil dilation, aiding in fundoscopic exams, surgeries, and the treatment of various eye conditions [61].

- **Dexamethasone**

Dexamethasone, a potent steroid medication, possesses anti-inflammatory and immunosuppressant properties, exerting effects 25 times more potent than cortisol in its glucocorticoid function while having minimal mineralocorticoid impact. It can reduce the temperature gradient between the core and skin by regulating the immune response and decreasing the release of vasoconstrictors and pyrogenic cytokines. Studies have shown that dexamethasone can significantly decrease the incidence of shivering during spinal anesthesia, often outperforming other medications like

pethidine, with a reduced shivering rate of 10% compared to 37.5% in the pethidine group. Various studies using different doses of dexamethasone have consistently shown its effectiveness in reducing shivering incidence, even at very low doses, making it a valuable option in managing this complication during surgical procedures [62].

4. Future Prospectives:

First, the development of more precise patient risk assessment tools can enhance our ability to tailor prevention strategies. Personalized medicine, taking into account individual patient characteristics and genetic factors, may guide the selection of the most effective interventions. Furthermore, ongoing research into novel pharmacological agents and delivery methods holds promise for improved shivering management with fewer side effects. Combining the power of artificial intelligence and real-time monitoring could lead to predictive models that anticipate and preempt shivering events. Additionally, advancements in medical technology may offer innovative approaches, such as targeted temperature management devices and drug delivery systems. Collaborative efforts among anesthesiologists, surgeons, pharmacologists, and engineers are essential to further refine and optimize shivering prevention strategies, ultimately enhancing patient care and surgical outcomes in the context of spinal anesthesia.

5. Conclusions:

In conclusion, shivering remains a challenging and multifaceted concern during spinal anesthesia, impacting patient comfort, surgical outcomes, and healthcare resource utilization. This review article has provided a comprehensive overview of the mechanisms, risk factors, and an extensive array of prevention strategies, both non-pharmacological and pharmacological. While significant progress has been made in shivering prevention, there is no one-size-fits-all solution. Careful consideration of patient characteristics, surgical context, and potential side effects is paramount in selecting the most appropriate prevention method. The future holds promise for even more refined and personalized approaches, driven by advancements in medicine and technology. Through continued research and collaboration, the medical community can look forward to a future where shivering during spinal anesthesia becomes an increasingly manageable and rare occurrence, ensuring improved patient comfort and safety.

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